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			1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/767,088

Applicant(s)

GURNEY ET AL.

Examiner

Anne-Marie Falk, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 July 2004.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) 3-8 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2 and 9-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 January 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

The amendment filed July 20, 2004 has been entered. Claims 1, 10, 11, and 14-17 have been amended.

Claims 1-17 are pending in the instant application.

Claims 3-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the response filed November 3, 2003.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, Claims 1, 2, and 9-17 are examined herein.

The elected invention is drawn to a transgenic mouse comprising a polynucleotide encoding a human wild-type tau protein, wherein said tau protein is the isoform that is 352 amino acids in length.

The objection to the specification is withdrawn in view of the amendment to the specification.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Appropriate correction is required.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 16 and 17 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

Claim 16 is directed to a method of screening for a drug that blocks hyperphosphorylation of tau. The claim requires the use of a transgenic mouse expressing hyperphosphorylated tau protein. Claim 17 is directed to a method of screening for a drug that blocks formation of filamentous aggregates of tau. The claim requires the use of a transgenic mouse expressing human tau protein forming filamentous aggregates.

The specification does not provide a written description of a transgenic mouse expressing hyperphosphorylated human tau protein as recited in Claim 16 nor a transgenic mouse expressing human tau protein forming filamentous aggregates as recited in Claim 17. In the absence of a clear written description of the mice to be used in the screening assays, the written description requirement is not satisfied for the claimed methods of screening.

At page 7, paragraph 3 of the response, Applicants assert that they made "transgenic mice expressing different forms of human tau" and Applicants conclude that this demonstrates that they were in possession of the claimed invention because the specification teaches that overexpressing tau results in hyperphosphorylation based on the studies of other transgenic animals. Applicants point to paragraph

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[0006] of the specification at page 2 which refers to transgenic mice expressing human tau under the control of the human Thy-1 promoter or the murine HMG-CR promoter. However, describing **other** mice, that is transgenic mice known in the prior art having distinct transgene constructs from those described in the claims, does not satisfy the written description requirement because what must be described in the specification is the **claimed** invention. For purposes of written description, the invention is whatever is now claimed. The claimed invention recites the use of a transgenic mouse that has a particular phenotype, i.e. a mouse expressing hyperphosphorylated human tau protein and a mouse expressing human tau protein forming filamentous aggregates. The specification does not disclose the mice recited in the claims. Applicants further assert that the specification describes methods using mice either containing hyperphosphorylated tau or filamentous aggregates to identify drugs to block their formation. However, a wish to obtain a transgenic mouse having a particular phenotype is not equivalent to describing an actual mouse that exhibits the hoped-for phenotype.

At page 7, paragraph 4 of the response, Applicants state that "even though Applicants did not specifically demonstrate that the mice described in the Examples are hyperphosphorylated [sic] or form filamentous aggregates, the 'concept' of the claims is clearly expressed throughout the specification." Applicants conclude that one of ordinary skill in the art would readily accept that Applicants were in possession of the claimed invention at the time of filing. However, given that phenotype is unpredictable, it is not enough to describe a hoped-for phenotype when the invention is in actually producing a mouse that has that phenotype. Applicants are reminded that the claims cover a large genus of transgenic mice expressing any form of a human tau protein, including numerous wild-type and mutant forms, but the specification does not describe mice that express these various human tau proteins **and** exhibit the desired phenotype.

In the absence of a clear written description of the mice to be used in the screening assays, the written description requirement is not satisfied for the claimed methods of screening.

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Enablement

Claims 1, 2, and 9-17 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

The following factors have been considered.

Nature of the invention. The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein.

Amount of direction or guidance presented and the presence or absence of working examples. The instant specification discloses the generation of transgenic mice using the wild-type tau isoform 383 amino acids in length. The specification also discloses two types of transgenic mice each having a point mutation within the 383 amino acid isoform of tau (V337M and P332L).

State of the prior art and predictability of the art. The specification fails to provide an enabling disclosure for the preparation of the claimed transgenic mice, because the phenotype of a transgenic animal cannot be predicted.

The specification fails to provide an enabling disclosure for the preparation of the claimed transgenic mice because the guidance offered in the specification is not sufficient to teach one of skill in

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the art how to prepare the claimed transgenic mice exhibiting an appropriate phenotype. The mere capability to perform gene transfer in any given species is not enabling for the claimed transgenic animals because the desired phenotype cannot be predictably achieved by simply introducing a construct as recited in the claims. While gene transfer techniques are well-developed for a number of species, including the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse cannot necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). Wall (1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements, and may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). In the absence of specific guidance, the production of a transgene-dependent phenotypic alteration resulting from the introduction of a nucleic acid construct as recited in the claim, is unpredictable. Thus, given the limited working examples, the existence of any phenotypic alteration resulting from the

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introduction of a tau transgene into mice, is highly unpredictable. Given the limited working examples and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the claimed transgenic mice.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

Accordingly, given the demonstrated lack of predictability in the art, the limited guidance provided in the specification, the state of the prior art, the broad scope of the claims, the quantity of experimentation needed, and the limited applicable working examples, one of skill in the art would not be able to make and use the claimed invention without undue experimentation.

At pages 8-9 of the response, Applicants assert that the **generation** of transgenic mice is routine. Applicants seem to be under the impression that the rejection is based on unpredictability for **generating** a transgenic animal. Applicants state that "the present invention is clearly enabled by the specification because Applicants describe in the instant application the **generation** of transgenic mice" (emphasis added). Applicants further state that "Wall does not state that **generating** a transgenic animal would require undue experimentation" (emphasis added). At page 9, paragraph 2 of the response, Applicants arguments are exclusively directed to "methodologies to **create** transgenic mice" (emphasis added). However, the Examiner has already acknowledged that **gene transfer** is routine in the art (page 5 of the Office Action mailed 1/29/04). What is not predictable is the **phenotype** of a mouse produced by introducing a particular transgene construct. One cannot predict *a priori* the phenotype of a mouse comprising a mouse prion promoter linked to a gene encoding the 352 amino acid isoform of wild-type human tau, or any other transgene, for reasons of record. At page 9, paragraph 3 of the response, Applicants address the Sigmund reference. Applicants assert that "Sigmund does not state that one

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cannot generate a transgenic mouse of one's choosing, but rather that it may require the generation of more than one mouse before the desired phenotype is created." Contrary to Applicants' assertion, Sigmund does not state that "it may require the generation of more than one mouse before the desired phenotype is created." The reference is aimed entirely at a discussion of the unpredictable phenotypic effects caused by variation in the genetic background of transgenic mice. The reference does not state or imply that if one generates more transgenic mice one will eventually obtain the phenotype that is desired. It does state that "it is essential that several independent lines of mice, derived from founders with different insertion sites, are examined before a conclusion relating a phenotype to a specific pattern of transgene expression is made." This is far from suggesting that, by generating "more than one mouse" as Applicants suggest, one can produce or obtain whatever phenotype one wants. The reference further points out that "position effects can profoundly influence transgene expression and, therefore the observed phenotype" (page 1426, column 1, paragraph 2). Thus, the reference clearly discloses a variety of issues in the transgenic art that lead to the unpredictability of phenotype, which is the basis of the enablement rejection.

The rejection is maintained for reasons of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 9, and 14-17 are rejected and Claims 10-13 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 9, and 14-17 are indefinite in their recitation of "a 5' flanking sequence of said prior gene promoter" because the metes and bounds of both the flanking sequence and the 5' end of the promoter are not clearly set forth. Without defining a 5' endpoint for a promoter, the term "5' flanking

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sequence” does not make sense because one is left to wonder – 5’ of what? or flanking what? The art generally does not define a 5’ end of a promoter. Thus, one of skill in the art would not know where the 5’ end of the promoter lies. Is it at 0.1 kb, 0.5 kb, or 1 kb? Furthermore, there is no teaching in the specification with regard to the length of “a 5’ flanking sequence.” Thus, it could cover one nucleotide or the remainder of the chromosome. As an example, if one defined a particular promoter as 500 nucleotides upstream from the transcription start site, a DNA comprising 600 nucleotides upstream from the transcription start site would then be said to comprise the 500 nucleotide promoter plus 100 nucleotides of 5’ flanking sequence. However, when the endpoint of the promoter is undefined, the term “5’ flanking sequence” does not make sense and one of skill in the art would not be able to determine if even a 1 kb region includes any “5’ flanking sequence” at all.

Claims 10-13 remain indefinite in their recitation of “5’ flanking sequence” and “the initial, noncoding portion of the second PrP exon” because the metes and bounds of these regions are not clearly set forth.

At page 10, paragraph 2 of the response, Applicants assert that one of skill in the art would know that the “initial, noncoding region of the second PrP exon” refers to “the region of the second exon that does not code for any of the prion gene product.” Applicants are incorrect. The phrase clearly does **not** refer to the entire noncoding region of the second exon. The phrase only refers to a **portion** of the noncoding region, specifically the portion that constitutes the **initial**, noncoding region of second exon. However, the specification does not offer any definition telling the skilled artisan how much of the noncoding region would constitute what Applicants refer to as the “**initial**” noncoding region. Thus, the skilled artisan would not be apprised of the metes and bounds of Applicants invention. Applicants further allege that the boundaries of the region are “defined by the methods described in Example 1 of the specification. However, nonlimiting examples, by their very nature, cannot **define** a term in the claims. Clarifying claim language is required.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) The invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in—

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, and 9-13 stand rejected under 35 U.S.C. 102(a) as being anticipated by Ishihara et al. (November 1999, Neuron 24: 751-762).

The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein. As amended, Claim 1 now recites that the regulatory region comprises “a promoter of said prion gene, a 5’ flanking sequence of said prion gene promoter and the first PrP exon.”

Ishihara et al. disclose the production and characterization of transgenic mice expressing human Tau polypeptides. The authors overexpressed the 352 amino acid isoform of human tau in the central nervous system of mice using a transgene containing a tau cDNA driven by a mouse prion protein promoter. They report that the transgenic mice acquired an age-dependent tauopathy similar to FTDP-17, PSP, and ALS/PDC. They further observed argyrophilic intraneuronal inclusions of 10-20 nm filaments. Brain and spinal cord tau became insoluble and hyperphosphorylated in the transgenic mice. The authors point out that, since similar tau pathology occurs in Alzheimer’s disease (AD), studies of these transgenic

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mice may elucidate mechanisms that lead to the selective degeneration of neurons in AD. In the paragraph bridging pages 751 and 752, the reference discloses that the transgene was made using the mouse prion promoter from the MoPrP.Xho vector of Borchelt et al. (1996, Genetic Analysis: Biomolecular Engineering 13: 159-163). The MoPrP.Xho vector includes the mouse prion promoter (about 600 nucleotides upstream of the transcription start site), exon 1, intron 1, and exon 2 (up to the KpnI site) of the mouse prion protein gene (see Figures 1 and 2). Thus, the transgenic mice disclosed by Ishihara et al. comprise all the elements recited in the instant claims.

Thus, the claimed invention is disclosed in the prior art.

At page 12 of the response, Applicants point to Claim 1 as amended and state that "[n]one of the references cited by the Office discuss or even suggest a transgenic mouse where the polynucleotide encoding a human tau protein is operably linked to a regulatory region of mouse prion gene that comprises the prion gene promoter and 5' flanking sequence of the prion gene promoter, and the first PrP exon." On the contrary, for the reasons discussed above (and below), the references clearly disclose a transgenic mouse comprising all the elements recited in the claims. For example, Ishihara et al. discloses the use of the MoPrP.Xho vector of Borchelt et al., which comprises the mouse prion promoter (about 600 nucleotides upstream of the transcription start site), exon 1, intron 1, and exon 2 (up to the KpnI site) of the mouse prion protein gene (see Figures 1 and 2). Nothing more is required.

Claims 1, 2, and 9-13 stand rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,664,443 (Hutton et al.).

The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein. As amended, Claim 1 now recites that the regulatory region

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comprises "a promoter of said prion gene, a 5' flanking sequence of said prion gene promoter and the first PrP exon."

Hutton et al. disclose transgenic mice expressing the human Tau polypeptide under control of the mouse prion promoter. See Examples 5-7. Transgenic mice expressing the wild-type 441 amino acid isoform of tau, the wild-type 383 amino acid isoform, and the P301L mutant form of tau were produced. The reference further discloses that the mice exhibited a Tau pathology. The mice developed motor and behavioral disturbances and tau-positive neurofibrillary tangles (NFT) were identified in the diencephalon, brainstem, cerebellar nuclei, and spinal cord (column 18, line 44 through column 19, line 27). The reference discloses that the transgene constructs were generated by inserting their tau cDNA into the XhoI site of the MoPrP.Xho vector of Borchelt et al. (column 16, lines 60-66). The MoPrP.Xho vector includes the mouse prion promoter (about 600 nucleotides upstream of the transcription start site), exon 1, intron 1, and exon 2 (up to the KpnI site) of the mouse prion protein gene (see Figures 1 and 2). Thus, the mice disclosed by Hutton et al. comprise all the elements recited in the instant claims.

Thus, the claimed invention is disclosed in the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, and 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zehr et al. (October 1999, Society for Neuroscience Abstracts 25(1): 447.1) and Borchelt et al. (1996, Genetic Analysis: Biomolecular Engineering 13: 159-163).

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The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein. As amended, Claim 1 now recites that the regulatory region comprises "a promoter of said prion gene, a 5' flanking sequence of said prion gene promoter and the first PrP exon."

Zehr et al. disclose the production and characterization of transgenic mice expressing human Tau polypeptides. The authors generated multiple lines of transgenic mice expressing one of four different tau cDNAs (wild-type 3 repeat, wild-type 4 repeat, V337M 3 repeat, and P301L 4 repeat). Expression of the tau polypeptides was driven by the mouse prion promoter. The highest levels of expression were found in the hippocampus, cortex, striatum, and the thalamus.

Borchelt et al. (1996) discloses an expression plasmid designated MoPrP.Xho. The expression vector includes the mouse prion promoter (about 600 nucleotides upstream of the transcription start site), exon 1, intron 1, and exon 2 (up to the KpnI site) of the mouse prion protein gene (see Figures 1 and 2). The reference further discloses several advantages of the MoPrP.Xho vector (page 162, column 2, paragraph 2). First, their studies showed that the level of transgene expression in brain is relatively proportional to the number of integrated transgene copies. Second, the authors point out that "because the entire open reading frame (ORF) of the prion protein gene is normally contained within a single exon, the replacement of the prion protein ORF with a recombinant cDNA ORF does not disrupt normal mRNA processing signals" (page 162, column 2, paragraph 2). On page 163, last sentence, the authors state that "[r]equests for the vector should be addressed to David R. Borchelt."

Given that a suitable vector comprising the mouse prion promoter was available in the art, and apparently readily available from the authors upon request, and further given that Zehr et al. disclose that mice expressing human tau in the brain can be generated by making transgenic mice where the transgene comprises the mouse prion promoter (moPrP) and a human tau cDNA, one of skill in the art would have

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been motivated to make tau transgenic mice using the readily available MoPrP.Xho vector of Borchelt et al. in order to investigate the consequences of human tau expression in the brains of mice. The skilled artisan would have anticipated a reasonable expectation of success because Zehr et al. had already generated transgenic mice that expressed human tau in various regions of the brain.

Furthermore, one of skill in the art would readily recognize that the tau transgenic mice of Zehr et al. were made using the MoPrP.Xho vector of Borchelt et al., as evidenced by their later disclosure in U.S. Patent No. 6,664,443, which provides additional details regarding the transgene present in the mice and explicitly states that the transgene constructs were generated by inserting their tau cDNA into the XhoI site of the MoPrP.Xho vector of Borchelt et al. (column 16, lines 60-66). Thus, the mice disclosed by Zehr et al. comprise all the elements recited in the instant claims.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 1, 2, and 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishihara et al. (October 1999, Society for Neuroscience Abstracts 25(1): 447.2) and Borchelt et al. (1996, Genetic Analysis: Biomolecular Engineering 13: 159-163).

The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein. As amended, Claim 1 now recites that the regulatory region comprises "a promoter of said prion gene, a 5' flanking sequence of said prion gene promoter and the first PrP exon."

Ishihara et al. disclose the production and characterization of transgenic mice expressing human Tau polypeptides. The authors overexpressed the 352 amino acid isoform of human tau in the central nervous system of mice using a transgene containing a tau cDNA driven by a mouse prion protein

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promoter. They report that the transgenic mice acquired an age-dependent tauopathy similar to FTDP-17, PSP, and ALS/PDC. They further observed argyrophilic intraneuronal inclusions of 10-20 nm filaments. Brain and spinal cord tau became insoluble and abnormally phosphorylated in the transgenic mice. The authors point out that, since similar tau pathology occurs in Alzheimer's disease (AD), studies of these transgenic mice may elucidate mechanisms that lead to the selective degeneration of neurons in AD.

Borchelt et al. (1996) discloses an expression plasmid designated MoPrP.Xho. The expression vector includes the mouse prion promoter (about 600 nucleotides upstream of the transcription start site), exon 1, intron 1, and exon 2 (up to the KpnI site) of the mouse prion protein gene (see Figures 1 and 2). The reference further discloses several advantages of the MoPrP.Xho vector (page 162, column 2, paragraph 2). First, their studies showed that the level of transgene expression in brain is relatively proportional to the number of integrated transgene copies. Second, the authors point out that "because the entire open reading frame (ORF) of the prion protein gene is normally contained within a single exon, the replacement of the prion protein ORF with a recombinant cDNA ORF does not disrupt normal mRNA processing signals" (page 162, column 2, paragraph 2). On page 163, last sentence, the authors state that "[r]equests for the vector should be addressed to David R. Borchelt."

Given that a suitable vector comprising the mouse prion promoter was available in the art, and apparently readily available from the authors upon request, and further given that Ishihara et al. disclose that mice expressing human tau in the brain and exhibiting a tau pathology similar to Alzheimer's Disease can be generated by making transgenic mice where the transgene comprises the mouse prion promoter (moPrP) and a human tau cDNA, one of skill in the art would have been motivated to make tau transgenic mice using the readily available MoPrP.Xho vector of Borchelt et al. in order to generate a mouse model of Alzheimer's Disease. The skilled artisan would have anticipated a reasonable expectation of success because Ishihara et al. had already generated transgenic mice that expressed human tau in the brain and spinal cord.

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Furthermore, one of skill in the art would readily recognize that the tau transgenic mice of Ishihara et al. were made using the MoPrP.Xho vector of Borchelt et al., as evidenced by their disclosure one month later in Neuron 24: 751-762 (November 1999), which provides additional details regarding the transgene present in the mice and explicitly states that the transgene constructs were generated by inserting their tau cDNA into the XhoI site of the MoPrP.Xho vector of Borchelt et al. (page 751, column 2, paragraph 4 to page 752, column 1, paragraph 1). Thus, the mice disclosed by Ishihara et al. (October 1999) comprise all the elements recited in the instant claims.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishihara et al. (October 1999, Society for Neuroscience Abstracts 25(1): 447.2).

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishihara et al. (November 1999, Neuron 24: 751-762).

The claims are directed to a method for screening for a drug for treatment of a neurodegenerative disease, or for a drug that blocks hyperphosphorylation of tau, or for a drug that blocks formation of filamentous aggregates of tau.

Ishihara et al. disclose the production and characterization of transgenic mice expressing human Tau polypeptides. The authors overexpressed the 352 amino acid isoform of human tau in the central nervous system of mice using a transgene containing a tau cDNA driven by a mouse prion protein promoter. They report that the transgenic mice acquired an age-dependent tauopathy similar to FTDP-17, PSP, and ALS/PDC. They further observed argyrophilic intraneuronal inclusions of 10-20 nm filaments. Brain and spinal cord tau became insoluble and hyperphosphorylated in the transgenic mice. The authors point out that, since similar tau pathology occurs in Alzheimer's disease (AD), studies of these transgenic

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mice may elucidate mechanisms that lead to the selective degeneration of neurons in AD. In the paragraph bridging pages 751 and 752, the reference discloses that the transgene was made using the mouse prion promoter from the MoPrP.Xho vector of Borchelt et al. (1996, Genetic Analysis: Biomolecular Engineering 13: 159-163). The MoPrP.Xho vector includes the mouse prion promoter (about 600 nucleotides upstream of the transcription start site), exon 1, intron 1, and exon 2 (up to the KpnI site) of the mouse prion protein gene (see Figures 1 and 2). Thus, the transgenic mice disclosed by Ishihara et al. comprise all the elements recited in the instant claims.

Given the phenotype of the disclosed transgenic mice and further given that said phenotype correlates with a pathological hallmark of a number of neurodegenerative diseases, it would have been obvious to use the mice to screen for drugs that may be useful in treating a neurodegenerative disease. Moreover, given the observed hyperphosphorylated tau protein in the brain and spinal cord of the transgenic mice, the skilled artisan would have been motivated to use the mice to screen for drugs that block this pathological process. Likewise, given the observed formation of filamentous inclusions in the transgenic mice, the skilled artisan would have been motivated to use the mice to screen for drugs that block this pathological process.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

At page 13 of the response, Applicants allege that Ishihara does not discuss or even suggest a transgenic mouse as described in pending claim 1. On the contrary, for the reasons discussed above, the transgenic mouse of Ishihara comprises all the elements recited in the instant claims. The transgenic mouse comprises the mouse prion promoter (about 600 nucleotides upstream of the transcription start site), exon 1, intron 1, and exon 2 (up to the KpnI site) of the mouse prion protein gene (see Figures 1 and 2). Applicants further allege and that there is no motivation to make the transgenic mouse as it is recited

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in the claims. However, no motivation is required to **make** the transgenic mouse because the reference explicitly **discloses** the mouse.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
MARIE FALK, PH.D.
PRIMARY EXAMINER